Summary Review for Regulatory Action

Date	(electronic stamp)
From	Ann. T. Farrell, M.D., Division Director
Subject	Division Director Summary Review
NDA/BLA # Supplement #	125486
Applicant Name	Genentech USA, Inc.
Date of Submission	04/22/13
PDUFA Goal Date	12/22/13
Proprietary Name / Established Name	Gazyva/obinutuzumab/GA101/RO5072759
Dosage Forms / Strength	1000 mg/40mL (25mg/mL) single use vial
Proposed Indication(s)	For the treatment of patients with previously untreated chronic lymphocytic leukemia (CLL)
Action/Recommended Action for NME:	approval

Material Reviewed/Consulted OND Action Package for this cycle, including:	
Medical Officer Review	Hyon-Zu Lee, Pharm.D./Barry Miller, MSN, CRNP./Virginia Kwitkowski MS, RN, ACNP-BC
Statistical Review	Chia-Wen Ko, Ph.D./Lei Nie Ph.D.
Pharmacology Toxicology Review	Stacey Ricci, MSc,. Eng,/Haleh Saber, Ph.D. /John Leighton, Ph.D.
CMC Review/OBP Review	Mate Tolnay, Ph.D. /Chikako Torigoe, Ph.D./Laurie Graham, M.S./Marjorie Shapiro, Ph.D.
BMAB Review	Don Obenhuber/ Kalavati Suvarna, Ph.D. /Colleen Thomas, Ph.D./Patricia Hughes Troost, Ph.D.
Clinical Pharmacology Review	Joseph Grillo, Ph.D./Sarah Schrieber, Pharm.D./Julie Bullock, Pharm.D./Jeffrey Florian, Ph.D./Nitrin Mehotra, Ph.D./Nam Atiqur Rahman, Ph.D.
DDMAC	Richard Lyght, Pharm.D./Karen Rulli, Ph.D.
DSI	Anthony Orencia, M.D./Janice Pohlman, M.D./Kassa Ayalew, M.D.
CDTL Reviews	Virginia Kwitkowski, MS, RN, ACNP-BC
OSE/DMEPA	Kevin Wright, Pharm.D./Yelena Maslov, Pharm.D./Scott Dallas, RPh.
OSE/DRM	Robert Pratt, Pharm.D./Cynthia LaCivita, Pharm.D./Claudi Manzo, Pharm.D.

Signatory Authority Review Template

1. Introduction

On April 22, 2013, Genentech USA, Inc. filed a biologics licensing application (BLA) under section 351(a) of the Public Health Service (PHS) Act for obinutuzumab, GA-101. GA-101 is a recombinant fully humanized monoclonal antibody (IgG1κ) that binds to CD20 transmembrane antigen on the surface of malignant and non-malignant pre-B and mature B lymphocytes. The FDA therapeutic class designation is a CD-20 directed cytolytic antibody.

The applicant submitted a request to be designated as a Breakthrough Therapy and the designation was granted. The applicant has proposed the following indication: "for the treatment of patients with previously untreated chronic lymphocytic leukemia".

The clinical support for the proposed indication comes from a single randomized trial. Genentech conducted a single randomized, multi-center trial (BO21004/CLL11), entitled "An Open-label, Multi-center, Three Arm Randomized, Phase 3 Study to Compare the Efficacy and Safety of RO5072759 + Chlorambucil (GClb), Rituximab + Chlorambucil (RClb) or Chlorambucil (Clb) Alone in Previously Untreated CLL Patients with Comorbidities".

The application was complete upon submission and was filed as a priority review. The PDUFA goal date for the current submission is December 22, 2013.

Obinutuzumab is not marketed in any country.

2. Background

Chronic Lymphocytic Leukemia (CLL) is the most common leukemia in adults in the US, accounting for approximately 30% of all leukemias. CLL is a serious and life-threatening lymphoproliferative disorder. The median survival is 8-10 years although the natural course of CLL can be variable with survival time ranging from 2-20 years or more depending on whether the disease is aggressive or indolent. Despite available therapy which can produce remissions, there is no curative therapy except for an allogeneic stem cell transplant. Unfortunately not all patients with CLL will be candidates for an allogeneic transplant. Some patients will eventually die of the disease or complications of the disease. The median age at diagnosis is approximately 71 years of age. The majority of patients are asymptomatic at diagnosis. However some patients can present with or develop "B symptoms" including weight loss, fever and night sweats.

The Agency has approved the following products for the treatment of CLL: chlorambucil, cyclophosphamide, fludarabine, alemtuzumab, bendamustine, ofatumumab and rituximab. The exact wording of the CLL indications granted vary based on enrolled populations. Most recently full approval for the treatment of CLL has been granted based on an improvement in progression free survival (PFS).

GA-101 or obinutuzumab is the fourth monoclonal antibody application for the treatment of CLL. Obinutuzumab is the third CD-20 directed cytolytic antibody proposed for the treatment of CLL.

3. CMC/Device

The Office of Biotechnology Products (OBP) did not identify any issues that would have precluded approval. The reviews noted that the product is well-characterized and that the manufacturing processes are well-controlled and consistent. Facilities inspections (substance) performed did not uncover any issues that would have precluded approval and there are no current issues involving the drug substance or drug product manufacture that would preclude approval.

The following text is taken from Dr. Shapiro's review:

Obinutuzumab is a full length recombinant, humanized, immunoglobulin IgG1κ monoclonal antibody (GA101, huMAb <CD20>, RO5072759) that is directed to CD20, a membrane protein expressed on B lymphocytes. Obinutuzumab is comprised of (b) (4) *The total molecular weight of obinutuzumab is approximately* (b) (4) *Da,* (b) (4)

Obinutuzumab drug product is supplied as a sterile, preservative-free liquid solution at 25 mg/ml in 50 mL single-dose vials. Obinutuzumab drug product is formulated in 20 mM L-histidine (L-histidine and L-histidine hydrochloride (b) (4) *), 240 mM trehelose* (b) (4) *, and 0.02% (w/v) poloxamer 188, pH 6.0. The inclusion of 20 mM L-histidine* (b) (4) *while 240 mM trehelose* (b) (4) *The* (b) (4) *poloxamer 188 at 0.02% (w/v)* (b) (4) *. As supplied, the solution of obinutuzumab drug product has a clear* (b) (4) *colorless to slightly brownish appearance that* (b) (4) *It is supplied in single-use, 50 mL vials containing 1000 mg (nominal) obinutuzumab for intravenous (IV) infusion. The extractable volume of each vial is a minimum 40 mL.*

The intended long term storage temperature for obinutuzumab drug product is 2-8°C. The primary packaging components for obinutuzumab drug product consist of a

USP/Ph. Eur./JP Type 1, (b) (4) colorless (b) (4) glass vial that is sealed with a 20 mm (b) (4) laminated (b) (4) rubber stopper (b) (4) and crimped with a 20 mm aluminum seal, then fitted with a slip off plastic cap.

Obinutuzumab is diluted into 250 mL 0.9% saline PVC or non-PVC polyolefin infusion bags immediately prior to administration. The diluted infusion solution can be stored at 2- 8°C for up to 24 hours.

The obinutuzumab drug product vial does125486 not contain any overages.

A claim for a categorical exclusion from the Environmental Assessment (EA) requirement has been submitted under 21CFR section 25.31(c), which states that any application for marketing approval of a biologic product for substances that occur naturally in the environment, or supplement to such an application, is categorically excluded and ordinarily does not require an EA or an Environmental Impact Statement when there is not a significant alteration of the concentration or distribution of the substance, its metabolites or degradation product in the environment. The Sponsor states that no extraordinary circumstances exist with respect to this product. There is no indication that additional environmental information is warranted. The claim of categorical exclusion is deemed acceptable.

Also from Dr. Shapiro's review:
The dating period for obinutuzumab drug product shall be 36 months from the date of manufacture when stored at 2-8°C. The date of manufacture shall be defined as the (b) (4).

The dating period for obinutuzumab drug substance shall be (b) (4) from the date of manufacture when stored at (b) (4) ….

Obinutuzumab is diluted into 250 mL 0.9% saline PVC or non-PVC polyolefin infusion bags immediately prior to administration. The diluted infusion solution can be stored at 2-8°C for up to 24 hours.

The product quality team identified a need for additional microbial retention data which was submitted and reviewed during the cycle.

The following two recommendations are for PMCs:
A formal verification for hold times of (b) (4) from manufacturing scale samples for up to (b) (4) will be completed in December 2013. The final study report will be submitted to the Agency by February 28, 2014.

Submit a protocol for (b) (4) The protocol should include bioburden and endotoxin limits to demonstrate continued microbial control over (b) (4) The protocol should be submitted as a CBE-30 by 31 Dec

2013. Execute the protocol and provide the results in the annual report following the approval of the CE-30.

The initial launch will be using [redacted] (b) (4). Due to the need to expedite the review and approval of this BLA, the Agency worked with the Applicant to develop a plan for launch. Genentech stated early during the BLA review that they [redacted] (b) (4) if the BLA was approved earlier than the PDUFA goal date. The CMC review team agreed that the [redacted] (b) (4) for commercial launch. Without this agreement, [redacted] (b) (4).

I concur with the conclusions reached by the Office of Biotechnology Products reviewers regarding the acceptability of the manufacturing of the drug product and drug substance including the initial launch. There are no outstanding issues which would preclude approval.

4. Nonclinical Pharmacology/Toxicology

The following text is from Dr. Saber's review:

Pharmacology, safety pharmacology (combined with toxicology), pharmacokinetic, and toxicology studies were conducted in in vitro systems or in animal species. Genetic toxicology studies were not conducted or needed per ICH S6 guidance. Obinutuzumab does not bind to the target in rodents. Toxicology studies were conducted in the cynomolgus monkey, a pharmacologically relevant species, using the administration route and dosing regimens that adequately addressed safety concerns in humans. Obinutuzumab-related toxicities in animals included depletion of B lymphocytes and immunogenicity/ hypersensitivity reactions. Infection seen in some animals may be secondary to lymphocyte depletion and inflammation in multiple organs may be secondary to the immunogenicity. Anti-drug-antibody was formed in animals; however, this did not interfere with the study results as adequate exposure to obinutuzumab was obtained. There were no drug-related effects in male or female reproductive organs in general toxicology studies.

An enhanced pre- and post-natal development (ePPND) study was conducted in cynomolgus monkeys. Pregnant animals received weekly IV doses of obinutuzumab during the period of organogenesis and lactation and through postpartum Day 238. Obinutuzumab was not teratogenic in animals; however, B cells were depleted in the offspring. The B-cell counts returned to normal levels within 6 months of birth Pregnancy category C is recommended for Gazyva and is consistent with the labels for Rituxan and Arzerra, CD20-directed antibodies with similar findings in the reproductive toxicology studies.

I concur with the conclusions reached by the pharmacology/toxicology reviewer, the supervisory pharmacologist and Dr. John Leighton, acting division director of DHOT, that there are no outstanding pharm/tox issues that preclude approval.

5. Clinical Pharmacology/Biopharmaceutics

The Clinical Pharmacology review of this application did not identify any deficiencies which would preclude approval. The review team did not identify post-approval required testing.

From the teams' review:

Obinutuzumab's time-dependent clearance was found to decline with a half-life of approximately 17 days….
Mild or moderate renal impairment did not affect obinutuzumab exposure. There is insufficient data available to determine the effect of severe renal impairment or any degree of hepatic impairment on obinutuzumab exposure.

Serum samples from CLL patients in the phase 3 trial were tested during and after treatment for antibodies to Gazyva. Approximately 13% (9/70) of Gazyva treated patients tested positive for anti-Gazyva antibodies at one or more time points during the 12 month follow-up period. The presence of Gazyva in patient serum at the time of anti-therapeutic antibody (ATA) sampling can interfere with the ability of this assay to detect anti-Gazyva antibodies. As a result, data may not accurately reflect the true incidence of anti-Gazyva antibody development. Neutralizing activity of anti-Gazyva antibodies has not been assessed.

In her review Dr. Bullock noted:
The pharmacokinetics of obinutuzumab are complex due to the elimination of obinutuzumab by two clearance mechanisms; one time-dependent and the other linear (time-independent). At the start of treatment, the time-dependent clearance is predominant but reduces over time. At steady-state (approximately 4 months), the linear clearance dominates. The covariate analysis found that the rate at which the time-dependent clearance diminishes and the linear clearance predominates is affected by tumor size.

Dr. Bullock also noted:
There are no dose modifications or other instructions proposed for drug-drug interactions or special populations (e.g., renal impairment, hepatic impairment, age, race, gender, weight) at this time.

I concur with the conclusions reached by the clinical pharmacology/biopharmaceutics reviews that there are no outstanding clinical pharmacology issues that preclude approval.

6. Clinical Microbiology

N/A

7. Clinical/Statistical-Efficacy

I have read the primary and secondary reviews. Only one pivotal trial was submitted for the indication.

The following text is excerpted from the primary review:
This BLA was supported by efficacy and safety data primarily from a randomized, open-label, parallel-group, multicenter phase 3 trial (BO21004/CLL11, specifically stage 1a) comparing obinutuzumab in combination with chlorambucil (GClb) to chlorambucil (Clb) alone in previously untreated CLL patients. Trial BO21004/CLL11 was conducted at 155 centers in 24 countries. A total of 356 patients were randomized to Clb (n=118) and GClb (n=238) in stage 1a. Randomization was stratified by Binet stage and region. The primary endpoint was investigator assessed PFS. However, for regulatory decision the primary endpoint of PFS was to be based on the results from the Independent Review Committee (IRC).

At the clinical cutoff on July 11, 2012 the median observation time was 14.2 months and median exposure to the study medications was 6 cycles. The IRC assessed median PFS was 11.1 months in the Clb arm versus 23.0 months in the GClb arm. The hazard ratio (HR) was 0.16 (95% CI: 0.11, 0.24), log-rank p-value <0.0001. At one year, 36% of patients in the Clb arm and 83% of patients in the GClb arm were progression free. All pre-specified sensitivity analyses for PFS were supportive of the primary analysis with HRs ranging from 0.12 to 0.26 and subgroup analyses of PFS were in general consistent with the ITT population (HRs ranged from 0.03 to 0.42).

Secondary endpoints included end of treatment response, best overall response, event free survival, duration of response, disease free survival, time to new anti-leukemic therapy and overall survival and were also supportive of the primary endpoints. However, there was no multiplicity adjustment plan for these endpoints. The best overall response rate was 32.1% in the Clb arm and 75.9% in the GClb arm (with CR rate of 0.9% in the Clb arm and 27.8% in the GClb arm). Among patients who had a response, the median duration of response was 3.5 months in the Clb arm and 15.2 months in the GClb arm [HR: 0.1 (0.05, 0.2), p-value <0.0001]…

The statistical review team also concluded with the clinical findings.

I concur with the conclusions of the clinical and statistical review teams regarding the demonstration of efficacy for the single indication for which licensure was sought.

8. Safety

The safety database was adequate.

The following text is excerpted from the primary review:

The main safety issues were infusion reactions and myelosuppression. Symptoms of infusion related adverse events were, in part, gastrointestinal, vascular including

hypotension and tachycardia, and respiratory. Infrequent important adverse events included tumor lysis syndrome, thrombocytopenia, and fevers. Though serious infections, such as Hepatitis B and PML, did not occur in this trial, there were cases in patients on other trials of obinutuzumab. The majority of adverse events occurred during the treatment period….

Conclusions
These risks are acceptable for a population with a life-threatening illness for which there is limited available therapy.

I concur with the recommendations of the clinical team.

Due to the observed infusion reactions, the Applicant revised the protocol dosing recommendations in order to prevent or lessen the severity of these reactions. The labeled dosing recommendations include premedication, dilution, recommendations not to push or rapidly administer and recommendations for either discontinuing if the patient experiences a grade 4 infusion reaction or steps to be taken with the next planned infusion.

9. Advisory Committee Meeting

This application was not taken to an Oncologic Drugs Advisory Committee meeting because there were no issues with the trial design, conduct, primary endpoint or data analysis. In addition the trial results demonstrated a positive risk benefit and no safety issues arose during the review of the application requiring an expert committee meeting.

10. Pediatrics

This is an orphan application. CLL is extremely rare in the pediatric population.

11. Other Relevant Regulatory Issues

The application complied with financial disclosure requirements. The Office of Scientific Investigations (OSI) determined that the data submitted appear reliable and can be used for decision-making.

There are no other unresolved relevant regulatory issues.

12. Labeling

The labeling was reviewed by all disciplines and consultant staff.

13. Decision/Action/Risk Benefit Assessment

- Recommended regulatory action

Approval for the following indication: for the treatment of patients with previously untreated chronic lymphocytic leukemia (CLL)

- Risk Benefit Assessment

The risk benefit assessment suggests that obinutuzumab in combination with chlorambucil is effective for the treatment of patients with previously untreated CLL based on the demonstration of a very substantial prolongation in progression free survival for the combination treatment compared with chlorambucil alone in an adequate and well-controlled randomized clinical trial. The major toxicities identified prior to approval include infusion-related reactions and myelosuppression. A favorable risk-benefit profile exists.

- Recommendation for Post marketing Risk Management Activities

No need for a REMS program -- routine post-marketing surveillance

- Recommendation for other Post marketing Study Requirements (PMR)/ Commitments (PMC)

We have asked the applicant:

Postmarketing requirements under 505(o) -None.

Draft postmarketing commitments not subject to the reporting requirements under section 506b

PMC #1

A formal verification for hold times of [redacted] (b) (4) from manufacturing scale samples for up to [redacted] (b) (4) will be completed in December 2013. The final study report will be submitted to the Agency by February 28, 2014.

PMC #2

Submit a protocol for [redacted] (b) (4) The protocol should include bioburden and endotoxin limits to demonstrate continued microbial control over [redacted] (b) (4) The protocol should be submitted as a CBE-30 by 31 Dec 2013. Execute the protocol and provide the results in the annual report following the approval of the CE-30.

For final versions of the PMRs and PMC see the approval letter.

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/s/

ANN T FARRELL
10/25/2013